



King's Research Portal

DOI:

[10.1192/bjp.bp.113.127191](https://doi.org/10.1192/bjp.bp.113.127191)

Document Version

Publisher's PDF, also known as Version of record

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Nair, A., & Howard, R. (2013). ENCODE and a new landscape for psychiatric genetics. *British Journal of Psychiatry*, 203(2), 84-85. <https://doi.org/10.1192/bjp.bp.113.127191>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Editorial

ENCODE and a new landscape
for psychiatric genetics

Akshay Nair and Robert Howard

**Summary**

Despite rigorous research into the genetics of neuropsychiatric disorders, the mechanism by which polygenic risk leads to complex clinical phenotypes remains unclear. The Encyclopedia of DNA Elements (ENCODE) project gives us new insight into gene regulation, and gene–gene and gene–environment interaction.

Better understanding of these key genomic mechanisms may provide the answers we have been searching for.

Declaration of interest

None.

Akshay Nair (pictured) is a NIHR Academic Clinical Fellow at the Department of Old Age Psychiatry, King's College London, Institute of Psychiatry. Robert Howard is Professor of Old Age Psychiatry and Psychopathology at the Department of Old Age Psychiatry, King's College London, Institute of Psychiatry.

Neuropsychiatric disorders such as schizophrenia demonstrate a high degree of heritability.^{1,2} Understanding the genetic component of these disorders has driven decades of rigorous research in psychiatric genetics.^{3,4} Building on the success of earlier techniques such as linkage studies, recent genome-wide association studies (GWAS)^{5–7} have begun identifying risk variants that may give us important insight into disease mechanisms. There remains, however, significant 'missing heritability'⁸ in these complex diseases. Findings from GWAS have also demonstrated that many risk alleles do not necessarily code for amino acid changes in proteins, indicating a more regulatory function.⁹ The role of gene–gene and gene–environment interactions in the expression of disease phenotype and timing of illness onset have been suggested, but with the exception of some epigenetic phenomena¹⁰ we understand relatively little about these mechanisms.

The significance of non-coding regions

The Encyclopedia of DNA Elements (ENCODE) project has assigned biochemical functions to 80% of the genome and in doing so has laid to rest the idea that the vast areas of non-protein-coding DNA discovered by the Human Genome Project is 'junk DNA'.¹¹ It has emerged that non-coding regions are involved in a large number of regulatory processes including gene–gene regulation, gene–protein interaction and the transcription of non-translated RNA.

By highlighting the importance of non-coding functional DNA, ENCODE will allow researchers to re-evaluate the significance of existing psychiatric GWAS findings. We already know that certain regulatory sites harbour GWAS variants that are strongly correlated with the promoter regions of genes associated with schizophrenia.¹² Regulatory elements close to neuronal growth genes are highly preserved in the human lineage, indicating previously unsuspected functional importance.¹³

Mechanisms for gene regulation, and gene–gene and gene–environment interaction

ENCODE found that 95% of the genome was within 8 kb of a protein–gene interaction.¹¹ These findings may frame new hypotheses for mechanisms of gene–environment interactions, why disorders associated with similar genetic risk⁵ present with varied phenotypes and why so many disorders have onset at specific points in life.

Protein coding accounts for only 2% of the genome and a further 75% can be transcribed into non-translated RNA, with a likely regulatory role in at least some cell types.¹⁴ The fundamental concept of what a gene actually is may require some rethinking¹⁵ and the role of non-translated segments of RNA in disease will be a new focus for medical genetics.

Finally, ENCODE has demonstrated how distant genes interact to affect each other,¹⁶ revealing what has been termed a '3D puzzle' of gene regulation.¹⁷ This may explain how multiple distant and unrelated genes interact to produce complex clinical phenotypes.

Conclusions

Psychiatry has good cause to feel excitement over ENCODE. Following decades of research into psychiatric genetics, few conclusive findings have been translated into clinical practice. Alongside the recent successes of modern psychiatric genetics, ENCODE offers a much greater appreciation of the complexity of genomic biology. In this new scientific landscape psychiatrists should find some important answers to long-asked questions.

Akshay Nair, BA, BMBCh, **Robert Howard**, MA, MD, MRCPsych, Department of Old Age Psychiatry, King's College London, Institute of Psychiatry, London, UK

Correspondence: Dr Akshay Nair, Department of Old Age Psychiatry, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK. Email: akshay.nair@kcl.ac.uk

First received 1 Oct 2012, final revision 30 Jan 2013, accepted 7 Feb 2013

References

- 1 Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Arch Gen Psychiatry* 2003; **60**: 1187–92.

- 2 Sullivan PF, Daly MJ, O'Donovan M. Genetic architectures of psychiatric disorders: the emerging picture and its implications. *Nat Rev Genet* 2012; **13**: 537–51.
- 3 Williams HJ, Owen MJ, O'Donovan MC. Schizophrenia genetics: new insights from new approaches. *Br Med Bull* 2009; **91**: 61–74.
- 4 Moore S, Kelleher E, Corvin A. The shock of the new: progress in schizophrenia genomics. *Curr Genomics* 2011; **12**: 516–24.
- 5 Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* 2009; **460**: 748–52.
- 6 Shi J, Levinson DF, Duan J, Sanders AR, Zheng Y, Pe'er I, et al. Common variants on chromosome 6p22.1 are associated with schizophrenia. *Nature* 2009; **460**: 753–7.
- 7 Genome-wide association study implicates HLA-C*01:02 as a risk factor at the major histocompatibility complex locus in schizophrenia. *Biol Psychiatry* 2012; **72**: 620–8.
- 8 Eichler EE, Flint J, Gibson G, Kong A, Leal SM, Moore JH, et al. Missing heritability and strategies for finding the underlying causes of complex disease. *Nat Rev Genet* 2010; **11**: 446–50.
- 9 Stefansson H, Ophoff RA, Steinberg S, Andreassen OA, Cichon S, Rujescu D, et al. Common variants conferring risk of schizophrenia. *Nature* 2009; **460**: 744–7.
- 10 Tsankova N, Renthal W, Kumar A, Nestler EJ. Epigenetic regulation in psychiatric disorders. *Nat Rev Neurosci* 2007; **8**: 355–67.
- 11 Bernstein BE, Birney E, Dunham I, Green ED, Gunter C, Snyder M. An integrated encyclopedia of DNA elements in the human genome. *Nature* 2012; **489**: 57–74.
- 12 Maurano MT, Humbert R, Rynes E, Thurman RE, Haugen E, Wang H, et al. Systematic localization of common disease-associated variation in regulatory DNA. *Science* 2012; **337**: 1190–5.
- 13 Ward LD, Kellis M. Evidence of abundant purifying selection in humans for recently acquired regulatory functions. *Science* 2012; **337**: 1675–8.
- 14 Djebali S, Davis CA, Merkel A, Dobin A, Lassmann T, Mortazavi A, et al. Landscape of transcription in human cells. *Nature* 2012; **489**: 101–8.
- 15 Ecker JR, Bickmore WA, Barroso I, Pritchard JK, Gilad Y, Segal E. Genomics: ENCODE explained. *Nature* **489**: 52–5.
- 16 Dostie J, Richmond TA, Arnaout RA, Selzer RR, Lee WL, Honan TA, et al. Chromosome Conformation Capture Carbon Copy (5C): a massively parallel solution for mapping interactions between genomic elements. *Genome Res* 2006; **16**: 1299–309.
- 17 Pennisi E. Genomics. ENCODE project writes eulogy for junk DNA. *Science* 2012; **337**: 1159–61.

BJPpsych

The British Journal of Psychiatry

ENCODE and a new landscape for psychiatric genetics

Akshay Nair and Robert Howard

BJP 2013, 203:84-85.

Access the most recent version at DOI: [10.1192/bjp.bp.113.127191](https://doi.org/10.1192/bjp.bp.113.127191)

References

This article cites 16 articles, 5 of which you can access for free at:

<http://bjp.rcpsych.org/content/203/2/84#BIBL>

Reprints/ permissions

To obtain reprints or permission to reproduce material from this paper, please write to permissions@rcpsych.ac.uk

You can respond to this article at

[/letters/submit/bjprcpsych;203/2/84](http://letters.submit/bjprcpsych;203/2/84)

Downloaded from

<http://bjp.rcpsych.org/> on April 29, 2016
Published by The Royal College of Psychiatrists
